PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32587A/UOC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/01984	International filing date *(day/month/year)* 23.05.2003	Priority date *(day/month/year)* 24.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/506		
Applicant UNIVERSITY OF CINCINNATI et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.02.2004	04.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Bazzanini, R Telephone No. +31 70 340-2970

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/01984

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-10

   because:

   ☒ the said international application, or the said claims Nos. 2-10 with respect to industrial applicability (Rule 67.1(iv) PCT) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,2,7-10 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6
	No:	Claims	1-4,7-10
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	See Separate Sheet
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III-1. No International Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

III-2. The subject matter of claims 2-10 (claims 3-6 and 10 inasfar as they refer to claims 2 or 7) relates to a method of treatment of human/animal body, which is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: HOME-PAGE OF THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, DEPARTMENT OF SURGERY, [Online] XP002251225 Retrieved from the Internet: <URL:http://www.surgery.wustl.edu/rs/resid ents.asp?subcategoryid=11&drid=204> [retrieved on 2003-08-13]

D2: WO 99 03854 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); BUERGER HANS MICHA) 28 January 1999 (1999-01-28) cited in the application

D3: FAGIN JAMES A: 'Perspective: Lessons learned from molecular genetic studies of thyroid cancer: Insights into pathogenesis and tumor-specific therapeutic targets.' ENDOCRINOLOGY, vol. 143, no. 6, June 2002 (2002-06), pages 2025-2028, XP002251224 June, 2002 ISSN: 0013-7227

D4: MERIC F ET AL: 'Expression profile of tyrosine kinases in breast cancer' CLINICAL CANCER RESEARCH 2002 UNITED STATES, vol. 8, no. 2, 2002, pages 361-367, XP002251226 ISSN: 1078-0432

V-1. The Applicant's attention is drawn to the fact that the present preliminary examination report expressed as to the novelty, inventive step and industrial applicability refers only to the matter for which an International Search Report has been drawn up, i.e. the compound of claim 1 and its monomethanesulfonate salt

(claims 9 and 10) in relation to the treatment of the real and defined diseases mentioned in claims 3-6.

V-2. For the assessment of the present claims 1-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V-3. NOVELTY:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims .1-4,7-10 is not new in the sense of Article 33(2) PCT.

V-3.1. From D1 it appears that Cohen et al. gave (oral) presentations on "inhibition of RET tyrosine kinase activity in medullary thyroid carcinoma by STI571 (Gleevec)" in at least 3 American or international conferences/meetings before the end of June 2002 (see page 2, paragraph 4,7,10).

D1 is therefore prejudicial to the novelty of claims 1-4,7,9.

V-3.2. D2 discloses the use of the claimed compound (mesylate salt of the compound of formula I, in the beta crystal form) in the treatment of a variety of tumours including breast cancer (see from page 3, paragraph 4 to page 4, paragraph 1; page 9, paragraph 3; page 10, paragraph 2; page 17, paragraph 1; examples 1-4,6). Breast cancer is known to be related to RET receptor tyrosine kinase from D3 (page 365, right column, paragraph 2).

Therefore, D2 is prejudicial to the novelty of claims 1,2,7-10

V-4. INVENTIVE STEP:

Should the applicant have overcome the above raised objection of lack of novelty, an inventive step could not be acknowledged over D1-D4 as the subject matter of claims 1-10, as far as novel, appears to be obvious over said documents (Article 56 EPC).

V-4.1. In fact, from D4 mutations of the RET protooncogene are known to be involved in multiple endocrine neoplasia type 2, familial medullary thyroid carcinoma, Hirschsprungs disease and human thyroid papillary carcinomas. RET tyrosine kinase represents therefore a target for drug development. STI 571 (imatinib mesylate), a small cell-permeable kinase inhibitor, has been successfully used in the treatment of chronic myelogenous leukemia thanks to its ability to inhibit abl

kinase. STI 571 is also effective against other kinases, and additional trials are planned to investigate the efficacy of imatinib mesylate to treat a variety of solid tumours whose pathogenesis is driven by the other tyrosine kinase targets.

D4 represent therefore a strong incentive to the use of imatinib mesylate in the treatment of those tumours related to the RET oncoprotein (see page 2025: left column paragraph 1, right column paragraph 2; page 2026: right column paragraph 2).

V-4.2. The claimed compounds (imatinib and its mesylate salt) have been already reported to be effective in a disease mediated by mutated-RET kinase, such as breast cancer (see D2 as illustrated by D3).

The claimed diseases are also known from D4 to be related to mutated RET-kinase.

Therefore, knowing about D2 the skilled person would, without any inventive effort, attempt to use imatinib or its mesylate salt in order to treat the mutated-RET related diseases mentioned in D4.